REMARKS

The Present Invention

The present invention pertains to isolated immunogenic peptides, compositions thereof, and methods of using the same.

The Pending Claims

Claims 100-137 are currently pending, of which claims 100-115 are directed to the isolated immunogenic peptides and derivatives thereof, while claims 116 and 117 are directed to compositions comprising the same, and claims 118-137 are directed to methods of using the compositions.

The Final Office Action

The Office has alleged that Figures 6, 7, and 9 disclose sequences, which lack a SEQ ID NO: tag. The Office has withdrawn claims 118-126 and 128-136 from consideration. The Office has rejected claims 100-106, 112-117, 127, and 137 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description and as allegedly lacking enablement. The Office has also rejected claims 100 and 116 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,679,511 (the '511 patent). The Office has objected to claims 107-111 as being dependent upon a rejected claim. Reconsideration of the objection and rejections is hereby requested.

The Amendments to the Specification and Claims

Figures 6, 7, and 9 have been amended to label appropriately the sequences disclosed therein with SEQ ID NO:s. Claim 100 has been amended to recite "[a]n isolated immunogenic peptide consisting of a portion of SEQ ID NO: 39, wherein said portion comprises (i) at least 9 contiguous amino acids from amino acids 56-70 of SEQ ID NO: 39, (ii) at least 9 contiguous amino acids from amino acids 448-462 of SEQ ID NO: 39, or (iii) a derivative of either of the foregoing, wherein the amino acid sequence of the derivative is at least 85% identical with (i) or (ii)" which is supported in the specification at, for example, page 8, lines 13-28. Claims 101-106 have been amended to recite "wherein the portion comprises" instead of "wherein the peptide consists essentially of" or "wherein the peptide is a peptide selected from the group consisting of...a peptide consisting essentially of." Claim 105 has been amended to recite "amino acids" in front of "450-455 and 457-462 of SEQ ID NO: 39" and "of SEQ ID NO: 39" after "amino acid

456." Separate documents setting forth the precise changes to the specification and claims, as well as the text of all pending claims, are enclosed herewith.

Drawing Amendments

The Examiner is requested to approve the accompanying replacement drawings. Figures 6, 7, and 9 have been changed by adding the appropriate SED ID NO: tag after a sequence.

Discussion of the Withdrawal of Claims from Consideration

The Office alleges that claims 118-137 are patentably distinct from cancelled claims 66, 67, 89, and 90, since the endpoints of the methods of the pending claims and of the cancelled claims are allegedly distinct. The Office, however, has allowed into prosecution claims 127 and 137, as the steps of these claims are identical to those examined in the previous office action. However, the steps of claims 118, 119, 123, 128, 129, and 133 are merely specific types of administration of peptides or compositions thereof, such that, if the Office has considered art pertaining to the administering steps of claims 127 and 137, then it is likely that the Office has already considered art that pertains to the patentability of other method claims. To the extent that this is true, Applicants request that such other method claims not be withdrawn from consideration.

Discussion of the Objection to the Claims

The Office has objected to claims 107-111 as dependent upon a rejected claim and has asserted that claims 107-111 are allowable if made independent of rejected claim 100. However, in view of the amendments made to claim 100, Applicants believe that this claim is in condition for allowance, such that claims dependent thereon, including claims 107-111, are also allowable. The objection to claims 107-111, therefore, is believed to be moot in view of the amendments made to claim 100.

Discussion of the Rejections under U.S.C. § 112, first paragraph

Claims 100-106, 112-117, 127, and 137 have been rejected under Section 112, first paragraph, as allegedly lacking written description. This rejection is traversed for the reasons set forth below.

The Office specifically alleges that the phrase "consisting essentially of" has been interpreted as "comprises" in view of what the Manual of Patent Examining Procedure (M.P.E.P.) at Section 2111.03 states. This interpretation is improper, as the M.P.E.P. states that "*absent a clear indication in the specification and claims of what the basic and*

novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to 'comprising' " (emphasis added). Contrary to what the Office asserts, the specification does, in fact, teach what the basic and novel characteristics of the immunogenic peptides actually are. They are the sequences of the peptides themselves, listed as SEQ ID NOs: 1-3, 5, 6, 8-14, 18, and 19. The recitation of "consisting essentially of" in the claims is meant to encompass peptides that have as an active immunogenic portion the sequences listed and may further comprise other amino acids that do not materially affect the functionality of the immunogenic portion of the peptide. Thus, if a peptide consists of SEQ ID NO: 1 and at either or both ends one or more additional amino acids, which do not interfere with the function of the immunogenic portion (SEQ ID NO: 1), then this peptide is encompassed within the scope of the claims, since the peptide consists essentially of SEQ ID NO: 1.

Furthermore, from the numerous examples of peptides listed in the specification at, for instance Figures 6 and 9, it is clear to one of ordinary skill in the art that the peptides of the instant claims are between 9 and about 34 amino acids in length. This size limitation of "peptide" is supported by the specification at, for instance, page 9, lines 7-10. In order to make it clear that this is what is meant by "peptide, " claim 100 has been amended to recite this size limitation. Specifically, claim 100 now recites "wherein the immunogenic peptide is less than 34 amino acids in length."

However, in order to advance prosecution and not in acquiescence of the rejection, claim 100 has been amended to recite the transitional phrase "consisting of" in lieu of "consisting essentially of."

The Office argues that the peptide derivatives, wherein the peptide derivative is at least 85% identical with the specified amino acids of SEQ ID NO: 39, immunogenic peptide, encompasses peptides with an indeterminate number and type of additional amino acids and can conceivably lack the anchor residues necessary to bind to the MHC Class II molecules. Yet this simply is not the case inasmuch as the claims require that the immunogenic peptides must be recognized by a $CD4^+$ T lymphocyte, which is restricted by an MHC Class II molecule.

Furthermore, as the peptides of claims 101-106 and 109-111 were all found to be particularly immunogenic (see, for instance, Figures 6 and 9), the present inventive peptide derivatives have been actually reduced to practice. The M.P.E.P. at Section 2163, Subsection I, states that an actual reduction to practice demonstrates that Applicants were in possession of the claimed invention at the time of filing the instant application, thereby meeting the written description requirement.

The Office contends that the scope of claims 114, 115, 117, and 137 is too broad, alleging that, because the instant specification discloses that the immunogenic peptides are presented by specifically HLA-DRB1*0401, the above claims should, therefore, encompass only this particular MHC molecule. Applicants point out to the Office that it is generally known in the art that multiple MHC molecules can bind to and, thus, present a given antigenic peptide (see Chicz, R.M. et al. (1993), *J. Exp. Med.* 178, 27-47; and Malcherek, G. et al. (1995), *J. Exp. Med.* 181: 527-536, which are incorporated into the instant application by reference), such that the antigenic peptide could be linked to any one of many MHC molecules, which bind to the peptide, in order for the peptide to be presented to a T lymphocyte. Applicants direct the Office's attention to the specification at page 45, line 33, through page 46, line 4, which states that "[t]he utility of these peptides in the prophylaxis and/or therapy of melanoma may not be limited to patients expressing the Class II MHC molecule DRB1*0401, as Class II-restricted peptides are often capable of binding to more than one Class II molecule." Furthermore, the Office even admits to the fact that more than one MHC molecule can bind to tyrosinase, as it states that "[t]yrosinase appears to be an antigen recognized [by] a variety of MHC molecules" (see the top of page 6 in Paper No. 35 and bottom of page 5 of Paper No. 40). Even though the data provided in the specification are directed to tyrosinase binding to HLA-DRB1*0401, the invention should not be limited to this MHC molecule only, since there is a reasonable likelihood of success it is likely that other MHC molecules will bind to the present inventive tyrosinase peptides, and only routine experimentation would be required to identify these other MHC molecules. Such routine experiments are taught in the specification at, for example, page 44, lines 1–20.

In view of the foregoing, Applicants submit that the claimed invention is adequately described in the specification, and the scope of the claims is not overly broad. Therefore, Applicants request that the rejection under Section 112, first paragraph, for alleged lack of description be withdrawn.

Claims 100-106, 112-117, 127, and 137 have been rejected under Section 112, first paragraph, as allegedly lacking enablement. This rejection is traversed for the reasons set forth below.

The Office specifically contends that, in view of Rammensee et al., which teaches that peptides recognized by MHC Class II restricted cells are between 12 and 25 amino acids, and in view of the open interpretation of "consisting essentially of, " the scope of the claims encompasses peptides that are larger than 25 amino acids in length, such that these peptides are not enabled, according to Rammensee et al. However, according to Chicz et al, *J. Exp. Med.* 178: 27-47 (1993), peptides within the range of 10 to 34 amino

acids also can be immunogenic. Furthermore, claim 100 has been amended to recite that the immunogenic peptide is less than about 34 amino acids in length. Moreover, as the specification (page 8, lines 13-28) teaches that the immunogenic peptides can be a portion of the tyrosinase amino acid sequence (SEQ ID NO: 39), one of ordinary skill in the art is equipped to make immunogenic peptides that are less than about 34 amino acids in length. For example, one could add amino acids of SEQ ID NO: 39 that are N-terminal to amino acid 56 of SEQ ID NO: 39 and/or the amino acids of SEQ ID NO: 39 that are C-terminal to amino acid 70 to the N- and/or C-terminus/termini of the immunogenic peptide containing amino acids 56-70 of SEQ ID NO: 39, such that the length of the entire peptide does not exceed 34 amino acids.

The Office asserts that the peptide derivatives could conceivably lack the anchor residues necessary to bind to the MHC Class II molecules. However, as stated above, the claims require that the peptides are recognized by $CD4^+$ T lymphocytes, which are restricted by an MHC Class II molecule.

The specification, furthermore, teaches one of ordinary skill in the art how to test whether or not an immunogenic peptide meets the functional limitation recited in the claims. See, for instance, page 33, line 7, through page 34, line 8.

In view of the foregoing, undue experimentation is not required of one of ordinary skill in the art to make and/or use the present invention. As stated in the previous Amendment and Response to Office Action, the specification is replete with guidance as to how to make and/or use the present inventive peptides (see, for example, page 17, line 25, through page 18, line 32, page 22, line 5, through page 28, line 27, and page 43, lines 5-13).

The Office alleges that claims 127 and 137 lack enablement, since there are no examples of administration to a mammal of the present inventive peptides. The Office further contends that undue experimentation would be required for one ordinarily skilled to practice a method of preventing melanoma without additional guidance and direction from the instant specification. Finally, the Office alleges that, in view of Rosenberg et al., which teaches that only TILs restricted by HLA-A24 have been shown to mediate tumor regression *in vivo*, the present inventive methods are not enabled.

However, as stated in the previous Amendment and Response to Office Action, a reasonable correlation between the ability to stimulate $CD4^+$ T lymphocytes *in vitro* and the ability to induce $CD4^+$ T lymphocytes to respond to melanoma does, in fact, exist. Applicants point out to the Office the Manual of Patent Examining Procedure (M.P.E.P.), Section 2107.03, Subsection I, which states the following:

> "As a general matter, evidence of pharmacological or biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility...An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or compositions, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. *The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted uses.*" (emphasis in italics added).

Furthermore, the specification is replete with guidance as to how to administer to a mammal a peptide of the present invention, or a composition comprising the same, at, for example, page 19, line 13, through page 28, line 27.

The Office's contention that undue experimentation would be required for one ordinarily skilled to practice a method of preventing melanoma without additional guidance and direction is improper, since the pending method claims are directed to methods of inducing a $CD4^+$ T lymphocyte to respond to melanoma. In this regard, Applicants maintain that it would not require undue experimentation for one of ordinary skill in the art to practice the present inventive methods of inducing a $CD4^+$ T lymphocyte to respond to melanoma.

Furthermore, although Rosenberg, *Immunol. Today*, 18:178 (1997), discloses that "only TILs, [which recognize the tyrosinase antigen and which are] restricted by HLA-A24[,] have been shown to mediate tumor regression *in vivo*," this does not mean that HLA-A24 is the *only* MHC molecule by which TILs specific to the tyrosinase antigen are restricted. Other MHC molecules can mediate tumor regression *in vivo,* but these molecules had not yet been identified at the time of publication of Rosenberg et al. The data presented in the instant application demonstrate that TILs restricted by HLA-DR, namely by HLA-DRB1*0401, can also recognize immunogenic peptides, such that these TILs are likely to mediate tumor regression *in vivo*.

In view of the foregoing, Applicants submit that the peptide derivatives and the methods of the pending claims are enabled. Therefore, Applicants request that the rejection under Section 112, first paragraph, for alleged lack of enablement, be withdrawn.

Discussion of the Rejection under U.S.C. § 102(e)

Claims 100 and 116 have been rejected under Section 102(e) as allegedly anticipated by the '511 patent. In particular, the Office alleges that the '511 patent teaches a sequence (SEQ ID NO: 10), which *comprises* SEQ ID NO: 1 of the instant application (emphasis added). Since the Office interprets the phrase "consisting essentially of" as "comprising, " the Office contends that the '511 patent anticipates the present inventive peptides. This rejection is traversed for the reasons set forth below.

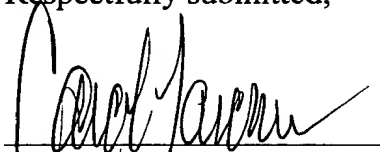
Applicants point out to the Office that claim 100 has been amended to recite the transitional phrase "consisting of," in addition to a length limitation, namely that the peptides are less than about 34 amino acids in length. Therefore, as the '511 patent clearly does not teach a polypeptide that is less than about 34 amino acids in length, the present invention is not anticipated.

In view of foregoing, Applicants submit that the '511 patent does not anticipate any of the peptides of the newly presented claims. Therefore, Applicants hereby request that the rejection under Section 102(e) be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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